

Nano-organotherapy: precision medicine with the natural organ-specific nano-sized proteins and peptides

Abstract

Organotherapy is a field of medical practice that uses animal-origin organ-specific extracts to treat the same organs in humans. This therapeutic modality has a long history, spanning from the empirical use of organ extracts in antiquity to the current application of nano-sized proteins and peptides. The main features of organotherapy are: (1) the use of a mixture of organ-specific proteins and peptides; (2) all active and inactive ingredients are derived from a natural source; (3) the concentration and combination of the ingredients correspond to the natural concentration and combination of these substances in a healthy organ. Although today the majority of the ingredients in organ-specific extracts can be identified, and their therapeutic effects can be explained, this information does not have a significant impact on the theory and practice of organotherapy. Since the effectiveness of any treatment depends not so much on the drug itself as on the treatment protocol, a theoretical comparison of the classical treatment approach, based on the physician's knowledge and experience, with a new one, which is termed the "evidence-based" approach, has been done. It is assumed that the more knowledgeable and experienced the physician practicing organotherapy, the higher the expected therapeutic effect and the greater the likelihood that the treatment can be classified as "precision medicine."

Keywords: nano-organotherapy, nano-peptides, nano-proteins, organotherapy, organ-specific extract, placenta extract, regenerative medicine treatments, thymus extract

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Introduction

As the name implies, "precision medicine" means effective treatment that uses an individualized protocol for delivering pharmaceutical or non-pharmaceutical treatments tailored to each patient according to his condition.¹ The primary benefit of this approach must be the high efficacy of the treatment.

"Precision medicine" is not a new approach, as it has been used for centuries. In different historical periods, different diagnostic methods and different criteria for prescribing individualized treatment were used. However, at present, it is possible to reveal the precise location of a disease, identify the main underlying pathogenic mechanisms, and, using genetic analysis, predict the location of a potential disease.

As we are aware, the formalization of the laws of nature has gone through a certain history. The basic discoveries in Mathematics and Physics were achieved in ancient times. Archimedes' law, ideas of inertia and atomic structure, or multiplication tables appeared thousands of years ago and they have not lost their value in the 21st century.

Ancient medical science had its canons too. The most important recommendations were: "to strengthen or reinforce that which is deficient, and drain or sedate that which is excessive". The derived rule was "to warm what is cold and cool what is hot."²

Organotherapy, as a part of the ancient medical system, was used to strengthen the function of an organ weakened by a chronic disease or aging, and the choice of animal provided a warming or cooling effect in relation to the diseased organ. Based on the common laws, as well as on the knowledge of the affinity of certain remedies for certain organs, ancient doctors could conduct effective individualized therapy, which could be termed "precision medicine" today.

Further discoveries have been added to the main canons, which were still in use. Maintaining continuity and development in Medicine was similar to Mathematics and Physics, but only until the sixteenth or seventeenth centuries. Since the time of the scientific and technological "revolution", everything that turned out to be incomprehensible (due to lack of knowledge) or not repeatable (due to lack of experience) has been discarded as a non-scientific heritage. Thus, professional incompetence was presented as an achievement of modern scientific thought.

A vivid example of ignoring the world's medical heritage was the account of the Swiss doctor Paracelsus (Philippus... von Hohenheim), who, at his first lecture at the University, publicly burned medical canons written by famous doctors like Galen, Avicenna, and others.³

Further development of medicine has not always followed the basic canons, and sometimes treatments were not targeted at the primary cause or the main pathogenesis of the disease.

Nowadays, despite the fact that deficient patterns are the main mechanisms for the development of most chronic diseases, especially in the elderly, antagonists, blockers, or inhibitors are used instead of tonic or supportive therapy. Before prescribing blocking or sedative therapy, patients are not tested to determine whether the corresponding target is in an excited state. Typical examples of ignoring the pathogenesis of diseases include prescribing inhibitors of the enzyme glucose-6-phosphatase or its precursors in patients with type 2 diabetes mellitus, calcium channel blockers in patients with arterial hypertension, and phosphodiesterase type 5 inhibitors in cases of erectile dysfunction.

In fact, as a result of treatment, a new pathological condition is formed, which neutralizes the secondary or tertiary mechanisms of the initial disease, although the primary cause and pathogenesis remain

untouched. As a result, despite active preventive and therapeutic measures, the number of patients with common chronic diseases steadily increases.

Materials and methods

A review of the literature devoted to the history, theory, and practice of organotherapy was conducted, from its empirical use in ancient times to its modern use in the form of organ-specific nano-sized proteins and peptides. Special attention was devoted to the therapeutic use of placenta and thymus extracts.

For the current study, the following database sites were used: <https://www.google.books.com/>, <https://pubmed.ncbi.nlm.nih.gov/>, and <https://archive.org/>. In the presence of similar publications, preference was given to the earliest ones.

Results

Organotherapy has been an important field of medicine throughout human history

From the known history of mankind, doctors have used various minerals, plants, and animal organs for the prevention and treatment of diseases. The prescription of these remedies were based on the results obtained in the course of clinical trials that lasted for centuries. One of the important medical laws stated that in case of a disease of a certain organ, remedies should be prepared from the same organ taken from a young animal.⁴

In the 16th century, German doctor Heinrich Cornelius Agrippa expressed a commonly held view: “And it is well known amongst Physicians, that the brain helps the brain, and lungs, the lungs”.⁵ The majority of books on *Materia Medica* published in Europe included large sections where the preparation of animal origin remedies were described.^{6,7} Application of animal-derived remedies continued to be a common practice until the end of the 18th century.⁸

After a short break therapeutic application of animal-origin drugs was revived in the late 19th century. In 1889, French physician C.-É. Brown-Séquard experienced the effects of an extract derived from dog testicles on himself and reported his successful results at the session of the French Medical Academy of Sciences.⁹

Some years later, the application of extracts prepared from animal organs and tissues was called “Organotherapy”. In 1893, Dr. Max Kahane of Germany defined organotherapy as “the use of organic tissues and of their extracts, as well as of organic juices for therapeutic purposes”. He explained that it is based “upon a rational physiological and experimental pathological foundation which warrants further research”.¹⁰ By the early 20th century, organotherapy was already widely used in Europe and the United States.¹¹

Scientific discoveries in the field of organotherapy

After the revival of organotherapy, isolation of the most active ingredients from organ-specific extracts began. As a result of those studies, hormones and hormone-like substances were discovered.¹² Gradually, a new field of medicine called Endocrinology emerged, and hormone replacement therapy became a part of the daily practice among physicians.¹³ However, research in the field of classical organotherapy continued. Among the important results of that field of study was the confirmation of the affinity of organ-specific extracts to certain organs, which was proven by using special dyes and isotopes.^{14,15}

In 2018, two reports were presented that described the biological effects of extremely low-concentration organ-specific nano-sized

proteins and peptides. In one study, proteins and peptides isolated from the testicular tissue of cattle (molecular weights ranging from 1.00 to 10.00 and 65.712 kilodalton) increased the motility of human spermatozoa in vitro by 50-70% and this effect persisted for several hours.¹⁶ In the second study, proteins and peptides isolated from the bovine ovarian tissue (molecular weights ranging from 0.80-6.00 and 66.69 kDa) improved the viability and maturation of follicles in ovarian tissue in vitro.¹⁷ In both studies, the concentration of the proteins and peptides did not exceed 0.01-0.001 ng/mL.

In 2019, samples of rabbit-derived organ-specific extracts were tested at Monash University Malaysia. The average content of peptides was around 110 µg/mL, and it varied from 89.42 to 130.93 µg/mL.¹⁸ Identification of proteins and peptides from a sample, derived from rabbit placenta, was performed using liquid chromatography-mass spectrometry (PEAKS Studio 7.0; Bioinformatics Solution Inc., Waterloo, ON, Canada). The test revealed various proteins and peptides, including the well-known profilin (10.607 kDa), acyl-CoA-binding protein (9.915 kDa), small muscle protein X-linked protein (9.397 kDa), ubiquitin (9.397 kDa), thymosin beta-4 (5.037 kDa), and others.¹⁹

Ancient classical and modern alternative approaches to treatment

Currently, while prescribing a drug, a doctor may follow two main approaches. The first approach, due to its long history, can be considered the classical option. The second approach has appeared relatively recently, so it can be considered an alternative option.

Ancient classical approach to treatment

Since ancient times, treatment has been carried out according to the classical scheme. It is assumed that at a medical school, a student receives the necessary medical knowledge, including the technique to collect symptoms, complaints, and medical history; making a diagnosis, including a definition of the etiology and pathogenesis of the disease; as well as pharmacology, including the specific and nonspecific effects of medicines, and selecting an individual treatment protocol. Thus, at first, a doctor identified the similarity of the existing symptoms with the standard description of the disease and made a diagnosis. Then the doctor identified the difference between the patient's condition and the standard description of the disease and prescribed the individualized therapy.

With the accumulation of knowledge and practical experience, the effectiveness of treatment carried out by a doctor gradually increased. Therefore, patients valued a knowledgeable and experienced doctor more than the medicine itself.

This classical scheme of treatment means the use of a protocol that is tailored to one particular patient. Therefore, such treatment belongs to the category of “precision medicine”. Sometimes it is referred to as “off-label therapy.”

Despite the high efficiency of the individualized therapy, its results will fall into the category of anecdotal cases and will not be considered a scientific study. When conducting a meta-analysis, these results will be rejected due to the “bad statistics.”

Modern or alternative approach to treatment

With the modern approach, a large group of patients with the same nosological diagnosis is formed. All patients in this group are treated with the study drug according to the standard protocol. In addition to the main group of patients, there is a control group of similar patients who undergo sham (placebo) treatment. After completion of the study,

the results in both groups are compared. The differences between the two groups are identified, and then a conclusion is made about the effectiveness of the study drug. Based on the results obtained, the tested drug is added to the list of the drugs recommended for the treatment of a particular disease, or it is removed from this list.

This alternative approach was borrowed from homeopathic physicians who were exploring their new remedies in the mid-19th century. That type of extensive trial was criticized by Dr. Rudolf Virchow, who was the ‘father’ of modern Pathology. He insisted that despite certain similarities in pathology discovered in different patients with a similar disease, each patient has his or her individual disease. Thus, instead of using statistics collected from large groups of patients, doctors should pay more attention to a detailed analysis of each particular case.²⁰

Nowadays, the primary challenge of such a study is selecting a physician with the necessary knowledge to prepare the study protocol and the relevant experience to form a homogeneous patient group in terms of the disease’s pathogenesis that corresponds to the drug being studied. Another challenge of such studies is physicians’ independence from the manufacturers of the drugs.²¹ Therefore, this type of research underscores the depth of knowledge, experience, and ethical qualities of the physicians, but not the effectiveness of the drug being studied.

Recently, this type of study has become a platform for “evidence-based medicine”. Perhaps the results of such studies can be recommended for use by doctors who have recently received their medical diplomas and do not have sufficient medical experience. It helps to reduce the likelihood of adverse reactions in patients during therapy. But an experienced doctor does not need standard treatment protocols.

If a doctor has enough knowledge and experience to recognize the pathogenesis of the disease, gather a homogeneous group, and choose the best medicine for this particular pathogenesis, in his study, the efficiency of the tested medicine should be close to 100%.

If a doctor carries out a study and obtains negative results, his background should be checked to determine if he already has positive results in the study field. If he had only negative results, it means he has just proven his incompetence again, and his negative results and conclusions should be ignored, despite the fact that the statistics were impeccable.

One can assume that there are no ineffective drugs, but there are doctors who don’t know how to use them.

Practical application of organotherapy

Until now, organotherapy has been used based on the classical approach. A doctor who already has a medical education undergoes additional training in organotherapy. He studies how to use organ-specific extracts to treat the corresponding organ in a patient. Such treatment is focused not on the nosological diagnosis, but on the localization of the primary and secondary pathological processes.

It has been proven by the previous generations of doctors that “the brain helps the brain, and lungs, the lungs”,⁵ so there is a relatively good understanding of what extract should be prescribed for chronic diseases of a certain organ. After collecting information from primary assessment and additional examinations, a doctor determines the sick organ as a whole, for example, the lung, liver, or pancreas. In the case of a complex organ like the brain, one can choose a specific part of the brain, for example, the pituitary gland, hippocampus, or substantia nigra. After that, the prescription itself is simple: the extract

of the liver is used to support the function of the liver, kidney - for kidney, lung - for lung, substantia nigra – for substantia nigra, and for hippocampus they use extract of hippocampus.

Organ-specific extracts are not used in cases of active inflammation or hyperfunction of the relevant organs. Logically, it is better to avoid prescribing organ-specific extracts in combination with a blocker, antagonist, or inhibitor if both of them target the same organ.

Thus, theory and practice of organotherapy with the use of organ-specific extracts is relatively clear. However, there are more questions dealing with the indications when a doctor is going to prescribe extracts that affect the entire body, particularly those derived from the placenta or thymus.

Application of placenta extract

A review published in 2012 listed the main indications when placenta extract was used. In particular, they used it for stimulating immunity, wound healing, reducing skin pigmentation, and treating female patients who suffered from gynecological disorders.²²

According to the research conducted by Dr. Emanuel Revici, the beneficial effect of the placenta extract in a group of patients who suffered from advanced cancer was observed only if the patient’s urine pH was acidic, but not alkaline.²³ Therefore, measurement of urinary pH may be an important criterion for patient selection while prescribing placenta extracts.

If a doctor is familiar with the theory of traditional Chinese medicine, he can use an additional algorithm for using placenta extract. In traditional Chinese materia medica, all therapeutics (herbs, minerals, or parts of animals) have specific effects, so they are divided into groups of antipyretics, diuretics, hypnotics, etc. In addition, each therapeutic affects heat production and has affinity to a specific organ. For example, human placenta extract has a warming effect and has an affinity to the liver, lungs, and kidneys.²⁴ Therefore, placenta extract is used for toning up and warming up effects, for example, in cases of fatigue (lack of ATP production) and symptoms that point to the “cold” disease (lack of heat production).

Meanwhile, it was noted that if blood uric acid is relatively high, the disease is accompanied by a set of symptoms, including red tongue, thirst, constipation, dark urine, etc., which point to excessive heat production or “heat” syndrome.²⁵ So, a blood test on uric acid may be an additional criterion for selecting patients who can be prescribed placenta extract. If blood uric acid is higher than the middle of the normal range, placenta extract is not recommended. If blood uric acid is lower than the middle of the normal range, placenta extract can be used for its specific or general beneficial effects.

Since a blood test for uric acid allows to identify groups of patients who, according to the ancient canon of medicine, require opposite (warming or cooling) therapy, one may assume that this test can be useful to form groups of patients, whose response to treatment with the same medicine may differ significantly.

Application of thymus extract

The Immunomodulatory effect of thymus extract was discovered by Dr. Leonard C. Wooldridge in 1888.²⁶ As we are aware now, the thymus is an important organ of the immune system; it is the source of thymus dependent T-cell immunity, which in turn has a regulatory effect on all other components of the immune system. Due to the degeneration process taking place in the thymus while aging, its activity gradually declines.²⁷

The main indication of thymus extract is T-cell immune deficiency, caused by infectious and non-infectious pathogens, and by aging. Before the application of the thymus extract, a blood test on immunity is recommended to define the initial immune status and to follow up on the results of treatment. If there is a combination of immunodeficiency with a chronic disease of a particular organ, then a combination of thymus extract and an extract of the related organ is used.

Recent application of thymus and spleen extracts revealed a positive tendency or even normalization of the initially increased tumor markers, including CA 19.9, CA-72.4, Cyfra 21-1, and PSA.²⁸

Prophylactic application of organotherapy

The preventive use of organotherapy is based on the same principle as the treatment: “the brain helps (*to prevent*) the brain (*disease*), and lungs, the lungs”.⁵ If, at a certain time of the year, for example, in the winter season, an exacerbation of a chronic disease occurs, for example, pyelonephritis, to prevent the disease, the patient is recommended to undergo treatment with kidney extract in the fall. If a patient is a heavy smoker, he could be recommended to take lung extracts, even if he doesn't yet have a confirmed lung disease. At the beginning of the epidemic, thymus extract can be recommended for elderly patients to support their immune system, which is affected by aging.

Given the rapid development of medical genetics, the preventive opportunity of organotherapy is becoming especially relevant. If revealed genetic traits indicate an increased risk of developing a disease in a particular organ, prophylactic use of extracts from the related organ may be considered justified, although proving the effectiveness of prophylactic treatment may take several decades.

Discussion

Although hormone replacement therapy is a part of organotherapy, there are some differences between these two fields of medicine, which can be demonstrated in the following study.

In 2002, Cussons et al. attempted to repeat the experiment reported by Dr. C.-É. Brown-Séquard in 1889. They prepared extracts from the testicles of young dogs according to the technique described by Dr. Brown-Séquard. They did not inject the testicle extract into either the elderly patients or into old animals. Assuming that testosterone was the main active ingredient of the extracts, they merely tested its concentration. Then they calculated the dose of testosterone that Dr. Brown-Séquard injected himself with and found that it did not exceed 200 ng per day. Since the standard therapeutic dose of testosterone used nowadays varies from 5 to 10 mg per day, it was concluded that all the described therapeutic effects could be explained by the placebo mechanism.²⁹ This study highlights a common error that could be the reason for the impossibility of repeating trials conducted by famous experts in the past. When testing old therapeutic modalities, it is necessary to have enough experience and strictly adhere to the described protocol, but not stop halfway.

To understand the cause of the erroneous conclusion, one should recall that the natural testosterone is highly active compared with the inactive natural epitestosterone. The difference between them lies only in the angle of rotation of the OH group relative to the axis of rotation in the C-17 position. All artificial drugs used for testosterone replacement therapy have differences in the chemical formula and molecular mass compared with natural testosterone.³⁰ Thus, it is logical to suggest that an effective dose of artificial testosterone will always be higher than a therapeutic dose of the natural one.

Conclusion

Throughout human history, medicine has always been scientific, effective, and modern for that time. The proof of this statement is the fact that humanity has survived to this day, despite repeated wars, epidemics of infectious diseases, as well as natural disasters.

Organotherapy, as a field of medicine, has also gone through a long history from the empirical use of organspecific extracts in antiquity to the use of nano-sized peptides today. The main features of organotherapy are (1) the use of a mixture of ingredients, i.e., “biochemical noise”; (2) all active and inactive ingredients are derived from a natural source; (3) the used concentration and combination of the ingredients correspond to the natural concentration and combination of these substances in a healthy organ.

Since the effectiveness of any treatment depends on the competence of the physician, the more knowledgeable and experienced the doctor who practices organotherapy is, and the more diagnostic methods he uses to determine the primary localization and the pathogenesis of the disease, the higher the expected therapeutic effect, and the greater the likelihood that the treatment can be attributed to “precision medicine.”

Disclosures

The author has declared that Bionion Sdn Bhd. promotes various products and technologies related to regenerative medicine, including organ specific nano-peptides.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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